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Application No.	S2003/0515
Date of Filing	10 July 2003
Applicant	GALEN (CHEMICALS) LIMITED an Irish company of Belgard Road, Tallaght, Dublin 24

Dated this 13 day of July 2004.

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PATENTS ACT, 1992

The Applicant named herein hereby request

☐ the grant of a patent under Part II of the Act

☒ the grant of a short-term patent under Part III of the Act

on the basis of the information furnished hereunder.

1. **APPLICANT(S)**

Name(s) and Address(s) **GALEN (CHEMICALS) LIMITED**
Belgard Road
and **Tallaght**
Dublin 24
DescriptionNationality: **An Irish company**

2. **TITLE OF INVENTION**

"Intravaginal Drug Delivery Devices"

3. **DECLARATION OF PRIORITY ON BASIS OF PREVIOUSLY FILED APPLICATION FOR SAME INVENTION (SECTIONS 25 & 26)**

Previous filing date	Country in or for which filed	Filing No.
NONE		

4. **IDENTIFICATION OF INVENTOR(S)**
Name(s)/Address(es) and Nationality of person(s) believed by Applicant(s) to be the inventor(s)

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5. **STATEMENT OF RIGHT TO BE GRANTED A PATENT (SECTION 17(2)(B))**

By virtue of Deed of Assignment dated June 5, 2003

contd...../

(ii) ☒ specification containing a description and claims

☐ specification containing a description only

☒ Drawings referred to in description or claims

(iii) ☒ An abstract

(iv) ☐ Copy of previous application(s) whose priority is claimed

(v) ☐ Translation of previous application whose priority is claimed

(vi) ☐ Authorisation of Agent (this may be given at 8 below if this Request is signed by the Applicant(s))

7. **DIVISIONAL APPLICATION**

The following information is applicable to the present application which is made under Section 24 -

Earlier Application No:
Filing Date:

8. **AGENT**

The following is authorised to act as agent in all proceedings connected with the obtaining of a Patent to which this request relates and in relation to any patent granted -

Name
F. R. KELLY & CO.

Address
at their address as recorded for the time being in the Register of Patent Agents

9. **ADDRESS FOR SERVICE (IF DIFFERENT FROM THAT AT 8)**

GALEN (CHEMICALS) LIMITED

F. R. KELLY & CO.

By: Maura O'Connell
EXECUTIVE

Date: July 10, 2003

INTRAVAGINAL DRUG DELIVERY DEVICES

This invention relates to intravaginal drug delivery devices useful in the administration of pharmacologically active agents to a female of the human or animal species.

Although the following description relates primarily to intravaginal rings (IVRs), it is intended that the term intravaginal drug delivery device would embrace all device designs such as, but not limited to, ovoid or cylindrical devices.

Jackanicz [Jackanicz, T. M., Vaginal Contraception: New Developments. Harper and Row, Hagerstown, pp. 201-212, 1979)] teaches that several designs of intravaginal ring are possible for drug delivery in the vagina.

One device is that described as a "matrix" ring, in which the pharmacologically active agent is homogeneously distributed throughout the ring.

Another device is that described as a "shell" device, in which a pharmacologically active agent is dispersed in a reservoir, the reservoir being in the form of a narrow band or hollow annulus, sandwiched between a non-medicated central member and an outer non-medicated sheath which wholly surrounds the reservoir. This sheath acts as a metering, or rate-controlling, membrane. With this design, burst effects are reduced, when compared with the "matrix" ring. The "shell" design, with its outer non-medicated sheath, was originally introduced to permit faster release rates than those obtained from conventional "core" devices (see below). However, the disadvantage with the "shell" design is that the drug reservoir volume is limited, because of the non-medicated central member and the non-medicated outer sheath, so that sustained release over long periods is not possible due to drug exhaustion.

Another device is that described as a 'core' device in which the pharmacologically active agent is dispersed within a carrier system to form the reservoir, the reservoir being fully surrounded by a sheath designed to control the rate of release of the pharmacologically active agent from the device. In this design, high drug loadings are possible such that prolonged drug release can be achieved for up to twelve months from a single device. Burst release of drug is reduced, as compared to the aforementioned "matrix" ring design. Substantially zero-order release can be achieved due to the presence of the rate-controlling sheath. All commercially available intravaginal drug delivery devices are of "core" design and comprise a drug-loaded reservoir, wholly surrounded by a rate-controlling sheath.

International Patent Publication No. W0 01/70154 discloses a modified "core" ring design in which there is an open bore extending from the surface into the ring and an active agent-loaded core is then inserted into the open bore, following which the, or each, end of which open bore is then sealed with a cap. Thus, in this modified "core" design, the core is, in use, completely sealed by an outer sheath.

US-A-6,436,428 discloses a further modified "core" ring design, in which there is a bore extending into the ring, from the ring surface and there is a pharmaceutical composition comprising oxybutynin and an excipient, the composition being located in the bore. US-A-6,436,428 suggests that each free end of the bore is subsequently capped and the sealing of both ends of the bore is exemplified in Examples 3, 4, 6 and 8.

WO 99/56934 discloses controlled release devices (defined as at least one rate controlling membrane surrounding a core reservoir), prepared by co-injection moulding. Page 13 teaches that there may be small areas of exposed reservoir material at the entrance gate and/or the exit runner but, by controlling the injection parameters, "exposure of the reservoir material can be eliminated". WO99/56934,

concerning itself with controlled release devices, teaches away from considering providing an incomplete sheath, partly surrounding a core reservoir.

US-A-5,694,947 discloses a non-drug containing core member in the form of an open ring; and a drug containing delivery means, which encircles the core member, along part of its length, in a belt wise manner. The inner surface of the delivery means is in contact with a material which prevents migration of active agent into the core member. The delivery means may be surrounded with a membrane coating whose thickness may be adjusted.

Various physicochemical parameters control the rate of release of a pharmacologically active agent (drug) from any such intravaginal drug delivery device having an outer, rate-controlling sheath (see Chien [Novel Drug Delivery Systems, 2nd Edition, Chapter 2, pp 43-137 (Marcel Dekker)] which is incorporated herein in its entirety).

For the purposes of drug delivery from conventional intravaginal drug delivery devices, which are fully surrounded by rate-controlling sheaths, drugs are usually incorporated into the reservoir at sufficiently high concentrations such that most of the drug is present in the solid state. Before release can occur, individual molecules of the dispersed active drug(s) within the reservoir must first detach themselves from their crystal lattice, dissolve into the surrounding reservoir carrier system, diffuse to the surface of the reservoir and then diffuse through the sheath to the surface of the device. Once at the surface, the drug should then exhibit some aqueous solubility in order to partition into the aqueous diffusion layer consisting primarily of vaginal fluid, from which it then partitions into and across vaginal epithelium and, hence, into the systemic circulation.

The ability of the sheath to be rate-controlling is a function of the solubility and diffusivity of the drug within the sheath. The solubility of the drug in the sheath

is determined by its chemical structure/functionality, while the diffusivity of the drug through the sheath is related to its molecular size/volume/weight. Thus, drug solubility in the sheath and relatively small molecular size are thought to be important for significant delivery of a drug to the surface of such a device.

Unfortunately, the sheaths currently employed in the manufacture of intravaginal drug delivery devices are highly hydrophobic in nature [Polymeric Biomaterials: 2nd Edition, (Marcel Dekker) ed. Severian Dumitriu, pp 79-80 (silicone), p332 (poly(ethylene-co-vinyl acetate) and p328 (styrene/butadiene block copolymers)] and are thus best suited, when fabricated as the sheath of an intravaginal drug delivery device, for the intravaginal delivery of hydrophobic active agents such as steroids [AD Woolfson *et al.* Journal of Controlled Release, 61 (1999) 319-328; LGJ de Leede *et al.* Contraception 34 (1986) 589-602; SA Ballagh *et al.* Contraception 50 (1994) 517-533].

Problems arise in relation to relatively hydrophilic drugs which may not possess sufficient solubility in the sheath of the intravaginal drug delivery device, and/or whose molecular size/volume/weight are too large for rapid diffusion, to permit sufficient drug delivery to the device's surface and subsequent release. Generally, drugs with a molecular weight greater than 400 Daltons fall into this latter category. The difficulties are even more considerable when a daily release rate of the drug in the order of milligrams per day, is required.

Accordingly, to overcome these problems a new intravaginal drug delivery device is needed that allows relatively hydrophilic and/or relatively large molecular size/volume/weight drugs to be released from the device at suitable rates.

In the present invention, this is achieved through the use of intravaginal drug delivery devices in which at least part, but not all, of the reservoir is directly exposed to, in use, the vaginal environment. This results in shorter diffusional pathways for drug permeation compared with conventional sheath-enclosed

intravaginal drug delivery devices, where the drug must also diffuse through the sheath. Since sheaths are conventionally hydrophobic, this partial "by-passing" of sheath drug permeation permits a wider choice of reservoir carrier materials such as, for example, less hydrophobic carrier systems which, in turn, permits a wider choice of pharmacologically active agent(s).

Accordingly, the invention provides, in a first aspect, an intravaginal drug delivery device, comprising at least one reservoir, the, or each, reservoir containing at least one pharmacologically active agent or a prodrug thereof, dispersed in a carrier system; and a sheath, optionally an elastomeric sheath, discontinuously surrounding the reservoir. Said device may be of any dimensions compatible with intravaginal administration to the human or animal female.

Where the device is a pessary, the reservoir takes the form of a core of suitable shape for internalisation within the pessary sheath. Where the device is a "shell" ring device, the, or each, reservoir takes the form of a narrow band or hollow partial or full annulus. Where the device is a "core" ring device, the, or each, reservoir takes the form of a partial or full annulus. Optionally, the partial or full annular reservoir is coaxial, or concentric, with the "shell" or "core" ring device.

The sheath must discontinuously surround the reservoir in order that part, but not all, of the at least one reservoir is directly exposed, in use, to the vaginal environment. This can be achieved by the provision of one or more, optionally at least three or at least five, holes or openings, as will be described in greater detail hereunder. Alternatively, this can be achieved by filling the said holes or openings with further reservoir carrier material, which further reservoir carrier material can be the same or different.

The discontinuous sheath, where present, may be either of substantially constant thickness or may vary, as is desired.

Preferably, the sheath defines one or more, optionally three or more, holes extending through the sheath to the at least one reservoir, so that part of that reservoir is exposed, in use, to the vaginal environment (Figures 1A to H). These holes may extend to the surface of the at least one reservoir or may, in addition, extend at least partially into the at least one reservoir. These holes may be discrete holes of any shape or may be joined to give a continuous opening in the form of, for example, a slit. Such a slit may extend about the minor circumference of the torus-shaped ring, as shown in Figures 1 G or H or, alternatively, may extend about any major circumference of the torus-shaped ring, as shown in Figures 1 E or F, or, indeed, in any other orientation. The slit may be of any length up to the maximum inner or outer major or minor circumference of a ring device, depending on the location of the slit. Where discrete holes are present in the sheath, they may be present in any size, shape, number, alignment or distribution compatible with the daily rate of drug release required from the device and maintenance of the essential mechanical properties of the device.

More preferably, said holes or openings are present on the inner circumference of the intravaginal drug delivery device (Figures 1 B, F and H).

Even more preferably, said holes or openings are substantially cylindrical with a diameter in the range of about 0.5 to 5 mm, preferably about 1 to 3.1 mm.

Still more preferably, there are a plurality, for example 20 or less or optionally, 2 or 3 to 8 of said holes or slits aligned, optionally linearly, along the inner circumference of the intravaginal drug delivery device (Figures 1 B, F and H).

The, or each, hole or opening optionally is not in rectilinear or curvilinear alignment with the longitudinal axis of that reservoir. For example, the, or each, hole or opening may extend at an angle of about 10° to 170°, preferably about 20° to 160°, to the reservoir surface. In a device having a plurality of holes, the angle of each hole may be the same or different.

More particularly, the, or each, hole or opening may extend through the sheath at an angle of 70 to 110°, preferably substantially normal to the reservoir surface, but the orientation of the, or each, hole is not intended to be so limited. If the device is a ring device, the, or each, hole may extend substantially radially, inwardly or outwardly, through the sheath.

The device of the present invention may be a partial or complete toroid shape, preferably a partial or complete torus shape or a substantially cylindrical rod.

Optionally, the sheath may also contain a pharmacologically active agent or a mixture thereof.

The invention is schematically illustrated with reference to the accompanying drawings, in which:

Figure 1 shows perspective and transverse sectional views of various embodiments of the intravaginal drug delivery devices of the present invention;
Figure 2 shows the cumulative release of metronidazole from an intravaginal drug delivery devices having 0, 4 or 8 holes and containing 10% (w/w) metronidazole;
Figure 3 shows the cumulative release of metronidazole from an intravaginal drug delivery device having 0 or 8 holes and containing either 10% or 20% (w/w) metronidazole;
Figure 4 shows the cumulative release of metronidazole from an intravaginal drug delivery device having 0 or 8 holes and containing 10% (w/w) metronidazole with, or without, the presence of 30% (w/w) hydroxyethylcellulose in the core; and
Figure 5 shows the cumulative release of metronidazole from an intravaginal drug delivery device having 0 or 8 holes (internal or external) and containing 5% (w/w) metronidazole.

In a second aspect of the invention, there is provided a method of manufacturing an intravaginal drug delivery device according to the first aspect of the present invention, said method comprising the steps of combining at least one pharmacologically active agent, and at least one pharmaceutically acceptable carrier system, curing the whole and applying a sheath to discontinuously surround the reservoir.

In a third aspect of the invention, there is provided a method of manufacturing an intravaginal drug delivery device according to the first aspect of the present invention, said method comprising injecting or extruding a reservoir material into a hollow sheath. The sheath may be prior-provided as a discontinuous sheath or, alternatively, the sheath may be subsequently modified to form said discontinuous sheath.

Reservoir

The reservoir may be fabricated from any pharmaceutically acceptable carrier system. The reservoir carrier system should be, in use, solid or semi-solid, i.e. capable of conforming to the shape of the space available for the reservoir, e.g., fabricated from a material selected from a shape retaining material; a thermosetting material; or a thermoplastic material. For example, the reservoir carrier system may comprise an elastomeric or non-elastomeric, polymeric or non-polymeric, material. In any event, the reservoir carrier material must be biocompatible, i.e., suitable for insertion in the human or animal body.

The reservoir carrier system is chosen to achieve desirable drug release therefrom.

The dimensions of the reservoir are determined by such factors as the amount of drug to be delivered to the subject; the time period over which the drug is to be delivered; and the permeation characteristics of the drug.

Examples of suitable polymeric reservoir materials include, but are not limited to, siliconess, poly(ethylene-co-vinyl acetate), styrene-butadiene-styrene block copolymers, poly(hydroxyethylmethacrylate) (pHEMA), polyvinyl chloride, polyvinyl acetate, poly(vinyl alcohol), polyesters, poly(acrylic acid)s, polyethers, polyurethanes, polyacrylonitriles, polyethylene glycols, polyethylene, polypropylene, polymethylpentene, polybutadiene, cellulose and its derivatives and polyamides, and mixtures thereof. For example, pHEMA drug loaded reservoirs may be prepared by the free-radical polymerisation of an aqueous solution of hydroxyethylmethacrylate (HEMA, typically 10-50% by weight, crosslinking agent (0.5-5% by weight typically) and drug (0.1-30% by weight typically). The reservoirs thus produced are flexible, hydrophilic and provide rapid release of hydrophilic drugs.

Suitable non-polymeric reservoir materials include, but are not limited to, pharmaceutically acceptable low-melting point waxes such as stearyl alcohol or semi-synthetic glycerides of saturated fatty acids (preferably those of C_8 to C_{18}), or a mixture thereof. For example, the drug may be dispersed within a low-melting point wax and moulded at low temperature into a shape compatible with the intravaginal ring design.

Elastomers are preferred polymeric carrier materials. Elastomers are defined as amorphous, or predominantly amorphous, high molecular weight polymers above their glass transition temperature, which can be stretched and retracted rapidly, exhibit high strength and modulus when stretched, and recover fully whenever the stress is removed. Generally, these elastomers are crosslinked to restrain gross mobility, either permanently (a covalently-crosslinked elastomer), or reversibly (a thermoplastic elastomer). Elastomers are typically chosen from the room-temperature vulcanising type of organopolysiloxanes, for example, poly(dimethylsiloxane). Non-silicone elastomers that are known in the art include, but are not limited to, poly(ethylene-co-vinyl acetate) [Roumen FJME, Dieben TOM, Contraception, 59 (1999) 59-62] and styrene-butadiene-styrene

block copolymer [Vartiainen J, Wahlstrom T, Nilsson CG, Maturitas, 17 (1993) 129-137].

A preferred reservoir carrier system is derived from hydroxyl-terminated organopolysiloxanes (such as those disclosed in US-A-5,855,906) of the RTV (room temperature vulcanising) type, which harden to elastomers at room temperature or higher, following the addition of cross-linking agents in the presence of curing catalysts. The ability to crosslink at room temperature is, of course, desirable for the delivery of thermally sensitive pharmacologically active agents. Suitable cross-linking agents and curing catalysts are well known in the art. Typical curing catalysts would be the organic metal compounds such as stannous octoate, dibutyltin dilaurate, alkyl titanates and titanium chelates. The curing catalyst is chosen so as to be effective in the presence of the drug and not to interact chemically with the drug. Typical crosslinking agents would be alkoxysilanes such as tetraethoxysilane or n-propylorthosilicate (NPOS). Curing temperatures and times will vary, depending on the particular elastomer(s) used. For example, the curing temperature may vary between room temperature (15-25°C) and 150°C but is preferably within the range 60-90°C. The curing time may vary between a few seconds and several hours, depending on the elastomer(s) used. A preferred reservoir material is commercially available as Nusil Med 7.6382 from Nusil Technology, Carpinteria, California, USA.

Other suitable silicone elastomers suitable for intravaginal ring reservoir manufacture include addition-type, two-component poly(dimethylsiloxane)s which are platinum catalysed at room temperature or under elevated temperatures, one-component poly(dimethylsiloxane)s, and silicone elastomers functionalised with fluorine, benzyl and other moieties.

The reservoir, irrespective of its carrier material, may optionally contain one or more pharmaceutically acceptable excipients designed to further enhance the rate of drug release from the device. Examples include hydroxyethylcellulose, or

other water-soluble or water-swellable polysaccharides, preferably cellulose derivatives, glucose or other sugars, or water-soluble salts, proteins such as gelatin, nonionic surface active agents, bile salts, organic solvents, such as ethoxydiglycol, polyethylene glycol and fatty acid esters, preferably containing 2 to 20 carbon atoms, of which myristate esters are preferred.

Pharmaceutically acceptable fillers may be added to enhance the mechanical strength of the reservoir. For example, suitable fillers include finely divided, reinforcing or extending fillers such as high surface area fumed and precipitated silicas, clays such as kaolin, crushed quartz, diatomaceous earths, calcium carbonate, barium sulphate, iron oxide, titanium dioxide and carbon black. The proportion of fillers added will depend on the desired properties of the cured device but, usually, the filler content of the reservoir will be in the range 5-30 parts by weight per 100 parts by weight of the aforementioned reservoir carrier system.

Where the device is an intravaginal drug delivery device in the form of a ring, the reservoir may be a full reservoir, in that it forms a continuous (or annular) reservoir within the device, or it may be a partial reservoir, in that the reservoir is of a defined length, which is discontinuous. Optionally, more than one partial reservoir may be used in the same device, where each reservoir may contain the same pharmacologically active agent, different pharmacologically active agents, and/or more than one agent. Where one or more partial reservoirs are used, at least one, but preferably each, reservoir must be partially exposed, in use, to the vaginal environment via, for example, at least one hole extending from the surface of the sheath through to at least the surface of the at least one, but preferably each, reservoir.

It will be appreciated that at least some of the drug is released from the reservoir by diffusion of the drug through the reservoir carrier system. Among the important factors governing release from the intravaginal drug delivery devices of

the present invention are the solubility of the drug in the reservoir carrier system, the solubility of the reservoir carrier material and/or reservoir excipient in vaginal fluid, the surface area of the reservoir exposed to the vaginal environment and the distance the drug must diffuse within the reservoir carrier system to reach this "exposed" surface area.

Sheath

The sheath, which discontinuously surrounds the reservoir, comprises polymer which is biocompatible, i.e., suitable for insertion in the human or animal body. The sheath may, or may not, be capable of permitting the, or each, agent to diffuse therethrough. Polymeric and non-polymeric materials, as used in the aforementioned core, are also suitable for use in the sheath, whether or not they are elastomeric. For example, poly(ethylene-co-vinylacetate), styrene-butadiene block copolymers, polyurethanes, and silicones are mentioned, of which silicones are preferred. However, silicone elastomers need not be functionalised with fluorine.

More preferably, the polymer is an elastomer, particularly if the reservoir carrier system is not elastomeric. In this embodiment, the elastomeric properties of the sheath confer sufficient flexibility on the composite intravaginal drug delivery device to allow placement in, and retention within, the vagina. Most preferably, the polymer is a silicone elastomer derived from hydroxyl-terminated organopolysiloxanes (such as polydimethylsiloxanes) of the RTV type, which cure to elastomers at room temperature or higher, following the addition of cross-linking agents in the presence of curing catalysts.

Other suitable silicone elastomers suitable for intravaginal ring sheath manufacture include addition-type, two-component poly(dimethylsiloxane)s which are platinum catalysed at room temperature or under elevated temperatures,

one-component poly(dimethylsiloxane)s, and silicone elastomers functionalised with benzyl and other moieties.

Preferably, the sheath may also contain fillers to enhance the mechanical strength of the sheath. Fillers suitable for use in the reservoir are also suitable for use in the sheath. Usually, the filler content of the sheath will be in the range 0 to 30 parts by weight per 100 parts by weight of the sheath carrier system.

The sheath may also optionally contain one or more additional pharmacologically active agents.

The sheath may also optionally contain at least one pharmaceutically acceptable excipient designed to reduce or prevent drug release from the reservoir via diffusion through the sheath. Such excipients are often the same materials used as fillers, and act so as to increase the tortuosity of the diffusional path of the active agent, i.e., increase the diffusional distance that the active agent must traverse through the device prior to its release from said device. For example, suitable diffusion inhibitors include high surface area fumed and precipitated silicas, clays such as kaolin, crushed quartz, diatomaceous earths, calcium carbonate, barium sulphate, iron oxide, titanium dioxide and carbon black.

The sheath may further optionally contain at least one pharmaceutically acceptable chemical penetration enhancers designed to enhance drug absorption across the vaginal epithelium, for example, surface active agents, agents that have a reversible effect on the arrangement of epithelial lipids, such as oleic acid or agents that directly affect tight junctions between epithelial cells.

Device Geometry

The geometry of the device of the present invention may be chosen according to theoretical calculations by methods known to those skilled in the art such that the

desired daily release of the at least one pharmacologically active agent is achieved and sustained for the desired duration. For an intravaginal drug delivery device, the desired "geometry" would encompass, for example, the length, width and cross-sectional area of the device. For an intravaginal ring, the term "geometry" encompasses the overall diameter of the ring, the cross-sectional diameter of the ring and the length of the reservoir. Where the intravaginal ring is of "core" design, the term "geometry" also includes the ratio of the reservoir diameter to the diameter of the complete device in cross-section. A preferred geometry is a ring of "core" design having an overall or outer diameter of 45 - 60 mm, preferably 52-56mm; a reservoir diameter 1 - 6 mm, preferably 2-6mm; a cross-sectional diameter of 4 - 10 mm, preferably 6 - 10 mm; and a reservoir length of 2 - 150 mm.

Pharmacologically Active Agents

By "pharmacologically active agent" is meant any agent capable of defending against, or treating, a disease state in the human or animal body, or a prodrug thereof. Such agents are intended to be released into vaginal fluid by diffusion out of the intravaginal drug delivery device, and may exert their effect either locally or systemically. The active agent(s) may be hydrophilic or lipophilic, organic or inorganic material(s), which are prophylactically or therapeutically active.

By "prophylactic agent" is meant any agent (or its prodrug) effective in defending against a disease state in the human or animal body, preferably the human body.

By "therapeutic agent" is meant any agent (or its prodrug) effective in treating a disease state in the human or animal body, preferably the human body.

The terms "agent", "active agent" and "drug" are used herein interchangeably and are intended to mean any substance which falls within the definition of a

prophylactic agent or a therapeutic agent and which is capable *in vivo* of producing a desired, usually beneficial, effect.

Suitable prophylactic or therapeutic agents for use in reservoirs and/or sheaths in the devices of the present invention include, but are not limited to, the following:

- **Contraceptive drugs**

Desogestrel, Dienestrol, Diethylstilberol, Estradiol, Estriol, Estradiol-3-acetate, Ethinyl Estradiol, Etonogestrel, Gestodene, Levonorgestrel, Medroxyprogesterone, Medroxyprogesterone Acetate, Mestranol, Norethisterone, Norgestimate, Nonoxynol-9, Norethisterone Acetate, Progesterone, Testosterone, Testosterone Acetate, ST-1435 (a progestin), Tibolone

- **Pain and Migraine**

5HT-1 receptor blockers such as Almotriptan, Eletriptan, Frovatriptan, Naratriptan, Rizatriptan, Sumatriptan, Zolmatriptan

- **Drugs for hormone replacement therapy**

Dehydroepiandrosterone sulphate, Dienestrol, Diethylstilberol, Estrogens such as Estradiol, Estriol, Estradiol-3-acetate, Ethinyl Estradiol, Gestodene, Levonorgestrel, Luteinizing Hormone Releasing Hormone, Norethisterone, Norethisterone Acetate, Progesterone, ST-1435, Testosterone, Testosterone Acetate

- **Anxiety and Depression**

Selective Serotonin Reuptake Inhibitors (SSRIs)

- **PreMenstrual Syndrome**

Selective Serotonin Reuptake Inhibitors (SSRIs)

- **Drugs for genito-urinary disorders**

Flavoxate Hydrochloride, Propantheline Bromide, Tolterodine Tartrate

- Drugs for cervical ripening / induction of labour

misoprostol, oxytocin, PGE2, dinoprostone, nitric oxide donors(i.e., isosorbide mononitrate)

- **Antibacterial drugs**

Acrosoxacin, Amifloxacin, Amoxycillin, Ampicillin, Aspoxicillin, Azidocillin, Azithromycin, Aztreonam, Balofloxacin, Benzylpenicillin, Biapenem, Brodimoprim, Cefaclor, Cefadroxil, Cefatrizine, Cefcapene, Cefdinir, Cefetamet, Cefmetazole, Cefprozil, Cefroxadine, Ceftibuten, Cefuroxime, Cephalexin, Cephalonium, Cephaloridine, Cephamandole, Cephazolin, Cephradine, Chlorquinaldol, Chlortetracycline, Ciclacillin, Cinoxacin, Ciprofloxacin, Clarithyromycin, Clavulanic Acid, Clindamycin, Clofazimine, Cloxacillin, Danofloxacin, Dapsone, Demeclocycline, Dicloxacillin, Difloxacin, Doxycycline, Enoxacin, Enrofloxacin, Erythromycin, Fleroxacin, Flomoxef, Flucloxacillin, Flumequine, Fosfomycin, Isoniazid, Levofloxacin, Mandelic Acid, Mecillinam, Metronidazole, Minocycline, Mupirocin, Nadifloxacin, Nalidixic Acid, Nifurtoinol, Nitrofurantoin, Nitroxoline, Norfloxacin, Ofloxacin, Oxytetracycline, Panipenem, Pefloxacin, Phenoxymethylpenicillin, Pipemidic Acid, Piromidic Acid, Pivampicillin, Pivmecillinam, Prulifloxacin, Rufloxacin, Sparfloxacin, Sulbactam, Sulfabenzamide, Sulfacytine, Sulfametopyrazine, Sulphacetamide, Sulphadiazine, Sulphadimidine, Sulphamethizole, Sulphamethoxazole, Sulphanilamide, Sulphasomidine, Sulphathiazole, Temafloxacin, Tetracycline, Tetroxoprim, Tinidazole, Tosufloxacin, Trimethoprim and salts or esters thereof.

- **Antifungal drugs**

Suitable antifungal agents include Bifonazole, Butoconazole, Chlordantoin, Chlorphenesin, Ciclopirox Olamine, Clotrimazole, Eberconazole, Econazole, Fluconazole, Flutrimazole, Isoconazole, Itraconazole, Ketoconazole, Miconazole, Nystatin, Nifuroxime, Terconazole, Tioconazole, Undecenoic Acid and salts or esters thereof.

- Antimalarial agents

Chloroquine and Dapsone.

- **Antiprotozoal agents**

Acetarsol, Aminacrine, Azanidazole, Metronidazole, Nifuratel, Nimorazole, Ornidazole, Propenidazole, Secnidazole, Sinefungin, Tenonitrozole, Ternidazole, Tinidazole and salts or esters thereof.

- **Antiviral drugs, including antiretroviral agents**

AMD3100, N-Acetyl Cysteine, Abacavir, Aciclovir, 3'-Azidothymidine, BCH-10618, Brivudine, CD4, CD4-Ig2, CD4-PEG, CCR5 antagonists, C31G, Cantanospermine, Capravirine, Carrageenan, Cellulose Acetate Phthalate, Cidofovir, Curcumin, DAPD, Desciclovir, Dextrin Sulfate, 2',3'-Dideoxyinosine, 2',3'-Dideoxycytidine, Defensins, Didanosine, 1-Docosanol, Edoxudine, Efavirenz, Emivirine, Emtricitabine, Famciclovir, Fiacitabine, Gramicidin, Ibacitabine, Imiquimod, Immunoglobulins, Indinavir, Lamivudine, Loviride, Magainins, Nevirapine, Nonoxynol-9, Penciclovir, PRO 542, PRO 140, Protegrins, Procysteine, Ritonavir, Saquinavir, TMC-120, TMC-125, TMC-126, Tenofovir, UC-781, Valaciclovir, Valganciclovir and salts or esters thereof, Zalcitabine, Zidovudine

- **Drugs for treatment of endometriosis**

Danazol

- **Peptides for vaginal administration**

Adrenocorticotropic Hormone, Angiotensin, Beta-endorphin, Bombesin, Calcitonin, Calcitonin Gene Relating Polypeptide, Cholecystokinin-8, Desmopressin, Endothelin, Enkephalin, Gastrins, Glucagon, Human Atrial Natriuretic Polypeptide, Insulin, Luteinising Hormone Release Hormone, Melanocyte Stimulating Hormone, Muramyl-dipeptide, Neurotensin, Oxytocin,

Parathyroid Hormone, Peptide T, Secretin, Somatomedins, Somatostatin, Thyroid Stimulating Hormone, Thyrotropin Releasing Hormone, Thyrotropin Stimulating Hormone, Vasoactive Intestinal Polypeptide, Vasopressin, and their analogues or derivatives.

- **Anti-Emetic Drugs**

5HT3 antagonists, ondansetron,

- **Osteoporosis and/or hormone replacement therapy**

Selective Estrogen Receptor Modulators (SERMs)

- **Other potential drugs for vaginal administration**

Bromocriptine

Preferably, the, or each, drug is present in the reservoir in an amount of 1% to 65% (w/w) of the reservoir. Optionally, the, or each, drug is present in the sheath in an amount of 1% to 65% (w/w) of the sheath.

Intravaginal drug delivery devices of the present invention may be prepared by injecting or extruding a reservoir material into a hollow sheath. The sheath may be prior-provided with one or more holes or openings. Alternatively, said one or more holes or openings may subsequently be formed.

Intravaginal drug delivery devices of the present invention may alternatively be prepared by applying a sheath onto a solid reservoir. Once again, the sheath may be prior-provided with one or more holes or openings, or, alternatively, said one or more holes or openings may be subsequently formed.

The intravaginal drug delivery devices of the present invention need not be formed by co-injection of the reservoir material and the sheath.

Embodiments of the invention will now be demonstrated by reference to the following General Method of Manufacture, which are then exemplified by reference to Examples 1 – 4.

The invention is not limited to the embodiments described and exemplified herein, which may be modified and amended without departing from the scope of the present invention. Thus, for instance, it will be obvious to those skilled in the art that the technique of injection moulding referred to herein may be replaced in whole or in part by other manufacturing techniques that will produce the same end product, notably the technique of extrusion.

General Method of Intravaginal Device Manufacture

A hydrophobic elastomeric polymer containing about 25% (w/w) diatomaceous earth as a filler is provided. 97 parts by weight of this polymer is blended with 2.5 parts by weight of a cross-linking agent, n-propylorthosilicate (NPOS), to form an elastomer mix. A suitable hydrophobic elastomeric polymer is stannous octoate-cured polydimethylsiloxane polymer, a suitable example of which is that known as Nusil Med 7.6382.

85 parts by weight of the elastomer mix is further blended with 5 parts by weight of barium sulphate and the required number of parts by weight of the desired pharmacologically active agent(s), to form an active reservoir mix.

The reservoir of the intravaginal drug delivery device of the invention is prepared by mixing 200 parts by weight of the active reservoir mix with 1 part by weight of an activating catalyst, for example, stannous octoate. This mix may, if desired, be placed under vacuum to remove air. The resultant reservoir mix is injected into a reservoir mould and cured at 80°C for 2 minutes. Alternatively, the mix may be extruded, depending on its viscosity. The mould is then opened, following which the reservoir is removed and trimmed. It will be appreciated that, by the use of

different reservoir moulds, reservoirs of different lengths or diameters may be produced.

An intravaginal drug delivery device in the form of a complete torus-shaped ring is produced by mixing 200 parts by weight of the elastomer mix with 1 part by weight of an activating catalyst, for example, stannous octoate. The resultant full ring mix is injected into a full ring mould (designed with one or more projections such that corresponding one or more holes extend from the surface of the device at least to the surface of the reservoir will result when the final device is cured) containing the reservoir (full or partial length) prepared as previously described, and then cured at 80°C for 2 minutes. The mould is then opened, following which the full ring is removed and trimmed. A half or part ring could, equally, be prepared by using the required half ring or part ring mould. Furthermore, the full ring might be prepared by placing a pre-assembled half or part ring in the full ring mould and then injecting the full ring mix.

The moulds, which are preferably coated with, for example, Teflon (Trade Mark) or an electrolytically applied metalised coating, may be constructed of hardened carbon steel, stainless steel, aluminium, or any other material deemed to be appropriate. It will be appreciated that the mould design imparts the physical shape of the intravaginal drug delivery device, for example, a partial or complete ring, a rod or any other desired shape. Preferably, the device has a partial or complete toroidal shape, more preferably a partial or complete torus shape, or a substantially cylindrical shape.

The geometric characteristics of the device and the size, number, distribution, alignment and shape of the holes (openings) can be varied as required by the use of appropriately sized (and angled) inwardly extending projections from the moulds. Alternatively, the intravaginal ring device, or components thereof, may be prepared by extrusional processes, as will be obvious to those skilled in the art. Alternatively, the holes or openings may be introduced into a final ring device by

mechanical means, such as a bore device.

Protocol for *In Vitro* Release Studies

The *in vitro* daily release profiles for the intravaginal ring devices of the invention were determined under sink conditions in pH 5.0 acetate buffer. The term 'sink conditions' is intended to refer to that set of experimental conditions *in vitro* that effectively simulates the active haemoperfusion that occurs *in vivo*, and which results in a maximum drug diffusion rate, at any given time, across the aqueous boundary layer. Thus, the solubility characteristics of the drug will determine the choice of a suitable dissolution medium.

Release rates were determined in the following manner. Each intravaginal ring (n=4) was suspended in 100ml of the pH 5.0 acetate buffer in an individual stoppered 250 ml conical flask. The flasks were maintained at a constant temperature of 37°C in a shaking incubator. The contents of each flask were gently shaken at a constant rate (60 rotations per minute) selected to ensure the absence of a hydrostatic layer on the surface of the ring. The pH 5.0 acetate buffer was renewed every 24 hours (± 15 minutes) over a 14-day period. An aliquot (2 ml) of the used dissolution medium was analysed by high-performance liquid chromatography.

In the following examples, the geometry of the rings was as follows: 9 mm (transverse cross-sectional diameter), 54 mm (outer diameter), 5.5 mm (reservoir transverse cross-sectional diameter). The sheath thickness was 1.75 mm, and the cross-sectional diameter of each hole was 3.0 mm with a hole depth of at least 1.75 mm.

Example 1 (Influence of Number of Holes)

Intravaginal drug delivery devices in the form of a "core" design ring having a full

...gth (140mm) ...% (w/w) metronidazole reservoir (total drug content ~400 mg metronidazole) and either 0, 4 or 8 holes on the outer surface of the device were prepared by following the aforementioned General Method of Manufacture.

The influence of the number of holes on the cumulative *in vitro* metronidazole release from the rings is illustrated in Figure 2. Increasing the number of holes leads to an increase in the daily release rate, such that, after 14 days, the cumulative amounts released from the 0, 4 and 8 hole rings are 2.5, 6.0 and 10.9 mg, respectively.

Example 2 (Influence of number of holes and drug loading)

Intravaginal drug delivery devices in the form of a reservoir design ring having a full length 20% (w/w) metronidazole reservoir (total drug content ~800 mg metronidazole) and either 0 or 8 holes on the outer surface of the device were prepared by following the aforementioned General Method of Manufacture.

The influence of reservoir drug loading and number of holes on the cumulative *in vitro* metronidazole release from the rings is illustrated in Figure 3.

For the rings with no holes, the release profiles for the 10% and 20% (w/w) metronidazole-loaded rings are similar to each other, since it is the sheath which is controlling the release rate. Specifically, after 14 days, the cumulative amounts released from the 0 and 8 hole rings are 2.5 and 2.9 mg, respectively.

However, for the rings with an identical number and size of holes (8), release then becomes a function of drug loading. Increasing the reservoir metronidazole concentration from 10 to 20% (w/w) leads to an increase in the daily release rate, such that, after 14 days, the cumulative amounts released from the 10% and 20% (w/w) rings are 10.9 and 23.5 mg, respectively.

Example 3 (influence of addition of pore-forming excipient to drug loaded reservoir)

Intravaginal drug delivery devices in the form of a reservoir design ring having a full length, 10% (w/w) metronidazole plus 30% (w/w) hydroxyethylcellulose (HEC)-loaded reservoir (~400 mg metronidazole reservoir content plus ~1200 mg HEC reservoir content) and either 0 or 8 holes on the outer surface of the device were prepared by following the aforementioned General Method of Manufacture.

The influence of incorporating hydroxyethylcellulose, a hydrophilic pharmaceutical excipient, and the number of holes is illustrated in Figure 4.

For the ring with no holes, after 14 days, the cumulative amount released remains at 2.5 mg. The incorporation of 10% metronidazole, without or with, 30% (w/w) hydroxyethylcellulose into rings each having 8 holes leads to a significant increase in the amount of metronidazole released, such that, after 14 days, the cumulative amounts released from 0 and 30% (w/w) HEC-loaded reservoir rings are 10.9 and 54.9 mg, respectively.

Example 4

Intravaginal drug delivery devices in the form of a reservoir design ring having a full length 5% (w/w) metronidazole-loaded reservoir (~200 mg metronidazole reservoir content) and either 0 or 8 holes on the outer or inner surface of the device were prepared by following the aforementioned General Method of Manufacture.

Figure 5 demonstrates that the amount of metronidazole released *in vitro* from a 5% (w/w) metronidazole-loaded reservoir intravaginal ring is not dependent upon the location of the holes on the device surface. The release profiles for rings having holes on the external and internal surfaces are similar. Specifically, after

11 days, the cumulative amounts released from 3 (internal or external) hole rings are 7.4 and 7.5 mg, respectively.

The present invention is not limited to the embodiments described herein, which may be amended or modified without departing from the scope of the present invention.

CLAIMS:

1. An intravaginal drug delivery device comprising at least one reservoir, the, or each, reservoir containing at least one pharmacologically active agent or a prodrug thereof, dispersed in a carrier system; and a sheath discontinuously surrounding the at least one reservoir, so that, in use, at least part of the at least one reservoir is directly exposed to the vaginal environment.

2. An intravaginal drug delivery device according to Claim 1, in which the sheath defines one or more holes or openings, the, or each, hole or opening extending through the sheath to the at least one reservoir, so that at least part of the at least one reservoir is exposed, in use, to the vaginal environment.

3. An intravaginal drug delivery device according to Claim 2, in which the, or each, hole or opening may extend to the surface of the at least one reservoir or may, in addition, extend at least partially into the at least one reservoir.

4. An intravaginal drug delivery device according to Claim 2 or 3, in which the, or each, hole or opening may be of any shape or may be joined with an adjacent hole or opening to give a continuous opening in the form of a slit.

5. An intravaginal drug delivery device according to any one of Claims 2-4, in which the, or each, hole or opening is substantially cylindrical with a diameter in the range of about 0.5 to 5 mm, preferably about 1 to 3.1 mm.

6. An intravaginal drug delivery device according to any one of Claims 2-5, in which the, or each, hole or opening may extend through the sheath

substantially normal to the reservoir surface.

7. An intravaginal drug delivery device according to any one of Claims 2-6, in which the device is a ring device, and the, or each, hole extends substantially radially, inwardly or outwardly, through the sheath.

8. An intravaginal drug delivery device according to Claim 7, in which there are one to twenty, optionally three to eight, of said holes, optionally aligned linearly, along the inner circumference of the intravaginal drug delivery device..

9. An intravaginal drug delivery device according to any one of Claims 1-8, in which the device is a partial or complete toroid shape, preferably a partial or complete torus shape or a substantially cylindrical rod.

10. An intravaginal drug delivery device according to any one of the preceding claims, in which the reservoir additionally comprises at least one pore-forming excipient.

11. An intravaginal drug delivery device according to Claim 10, in which the pore-forming excipient comprises a water-soluble or water-swellable polysaccharide, preferably a cellulose derivative, more preferably hydroxyethylcellulose; a sugar, preferably glucose; a water-soluble salt; a protein, preferably a gelatin; a nonionic surface active agent; a bile salt; an organic solvent, preferably ethoxydiglycol or polyethylene glycol; or a fatty acid ester, preferably containing 2 to 20 carbon atoms, more preferably a myristate ester.

12. An intravaginal drug delivery device according to any one of the preceding claims, in which the sheath may also contain at least one pharmacologically active agent.

13. A method of manufacturing an intravaginal drug delivery device according to any one of the preceding claims, said method comprising the steps of dispersing at least one pharmacologically active agent in a pharmaceutically acceptable carrier system; curing the reservoir; and applying a sheath to partly surround the reservoir.

14. A method of manufacturing an intravaginal drug delivery device according to any one of the claims 1 to 12, said method comprising injecting or extruding a reservoir material into a hollow sheath.

Abstract

INTRAVAGINAL DRUG DELIVERY DEVICES

The invention relates to an intravaginal drug delivery device comprising at least one reservoir, the, or each, reservoir containing at least one pharmacologically active agent dispersed in a carrier system; and a sheath discontinuously surrounding the at least one reservoir, so that, in use, at least part of that reservoir is directly exposed to the vaginal environment. Preferably, the sheath defines one or more holes or openings, the, or each, hole or opening extending through the sheath to the at least one reservoir, so that at least part of that reservoir is exposed, in use, to the vaginal environment.

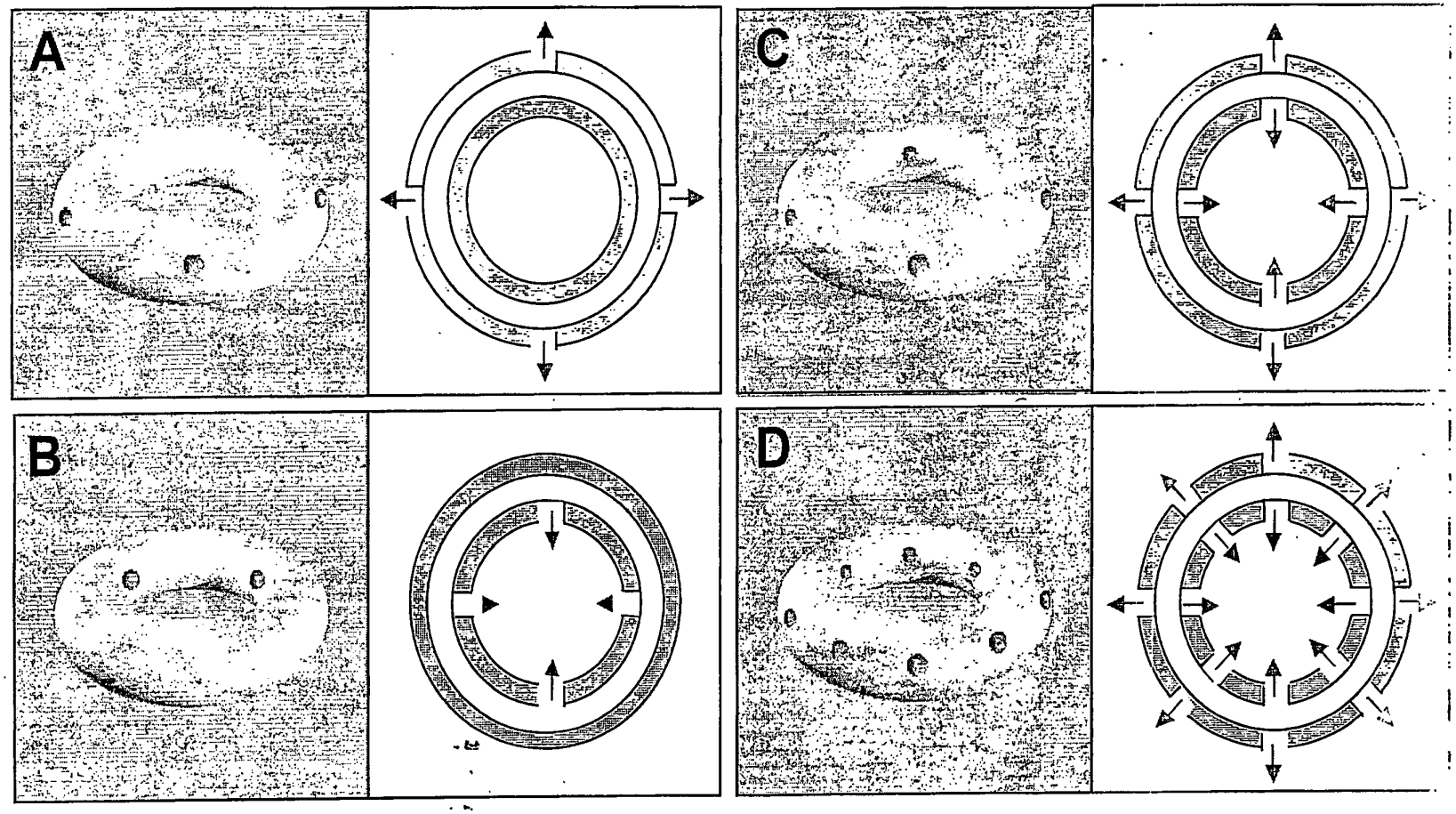

Figure 1. Perspective drawings and cross-sectional representations of: **A** - IVR with holes on outer surface, **B** - IVR with holes on inner surface, **C** - IVR with 4 holes on each of inner and outer surfaces, **D** - IVR with 8 holes on each of inner and outer surfaces

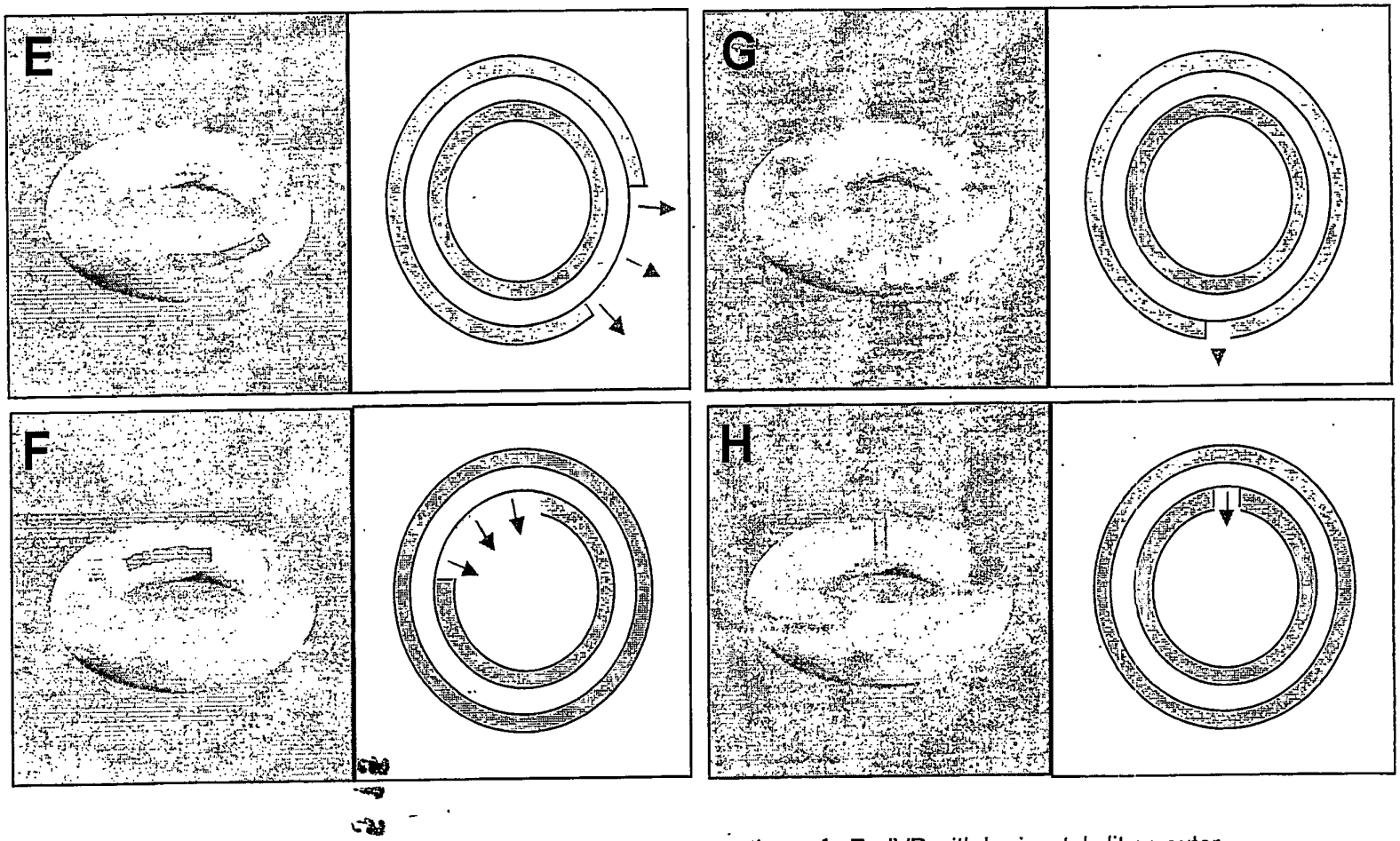

Figure 1 cont. Perspective drawings and cross-sectional representations of: **E** - IVR with horizontal slit on outer surface exposing drug -loaded core, **F** - IVR with horizontal slit on inner surface exposing drug -loaded core, **G** - IVR with vertical slit on outer surface exposing drug -loaded core, **H** - IVR with vertical slit on inner surface exposing drug - loaded core

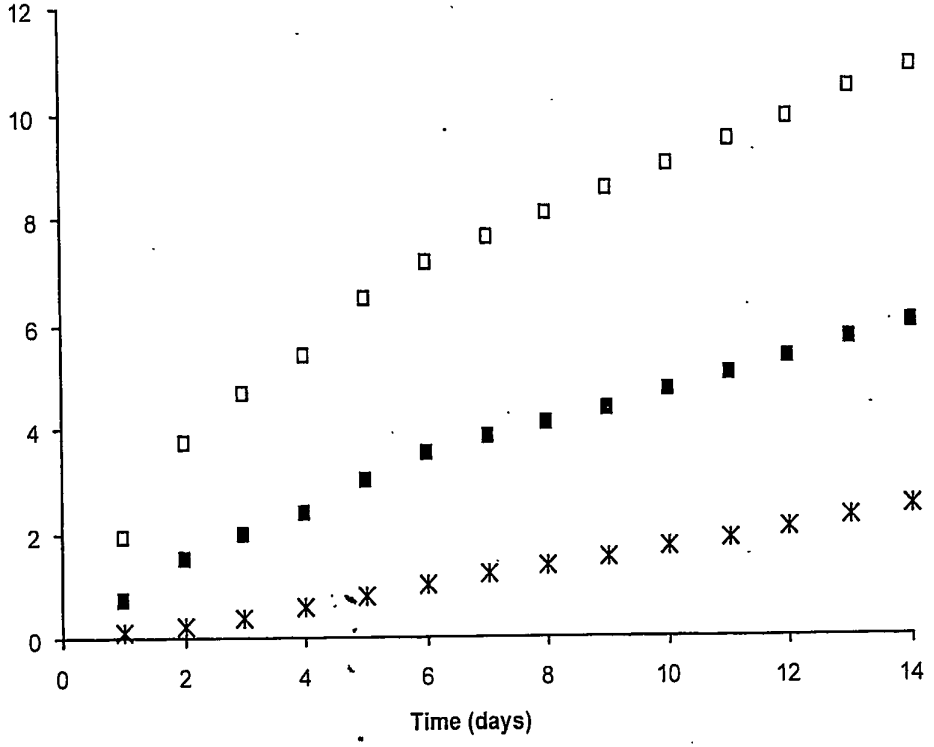

Fig. 2. Graph showing influence of **number of holes** on the cumulative release of metronidazole versus time for various intravaginal ring formulations
open squares – IVR with core containing 10% w/w metronidazole and eight external holes in sheath layer
filled squares – IVR with core containing 10% w/w metronidazole and four external holes in sheath layer
stars – IVR with core containing 10% w/w metronidazole and no holes in sheath layer

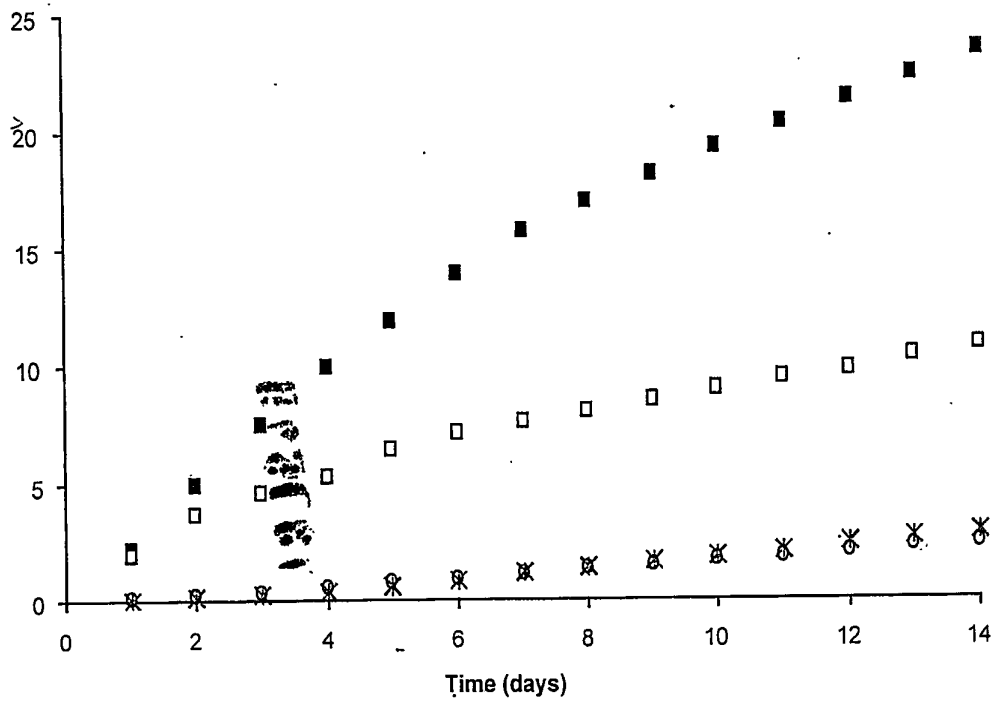

Fig. 3. Graph showing influence of **drug loading** on the cumulative release of metronidazole versus time for various intravaginal ring formulations
filled squares – IVR with core containing 20% w/w metronidazole and eight external holes in sheath layer
open squares – IVR with core containing 10% w/w metronidazole and eight external holes in sheath layer
stars – IVR with core containing 20% w/w metronidazole and no holes in sheath layer
open circles – IVR with core containing 10% w/w metronidazole and no holes in sheath layer

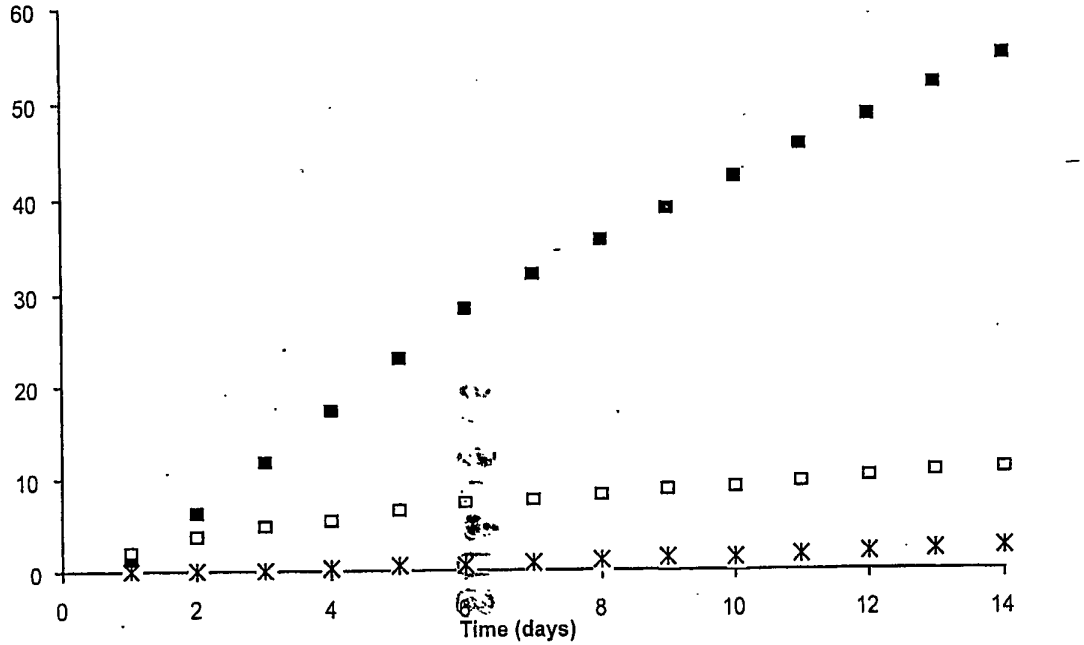

Fig. 4. Graph showing influence of **incorporation of excipient** on the cumulative release of metronidazole versus time for various intravaginal ring formulations

filled squares – IVR with core containing 10% w/w metronidazole and 30% w/w hydroxyethylcellulose and eight external holes in sheath layer

open squares – IVR with core containing 10% w/w metronidazole and eight external holes in sheath layer

stars – IVR with core containing 10% w/w metronidazole and 30% w/w hydroxyethylcellulose and no holes in sheath layer

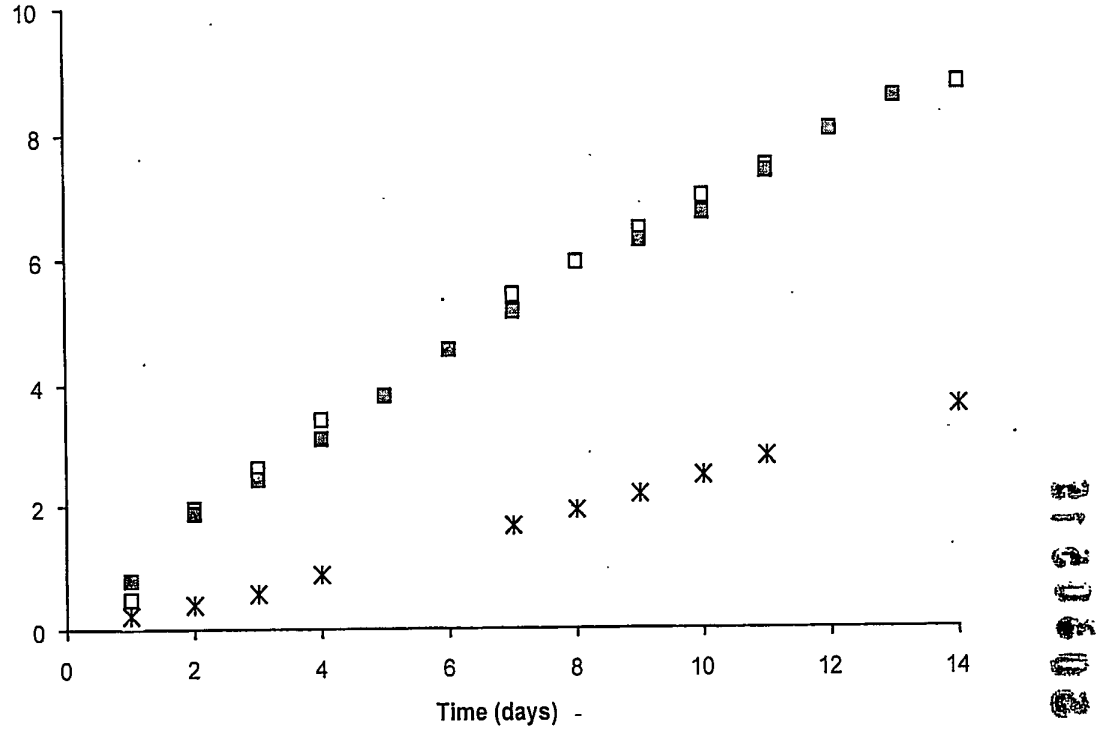

Fig. 5. Graph showing influence of **hole location** on the cumulative release of metronidazole versus time for various intravaginal ring formulations
filled squares – IVR with core containing 5% w/w metronidazole and eight internal holes in sheath layer
open squares – IVR with core containing 5% w/w metronidazole and eight external holes in sheath layer
stars – IVR with core containing 5% w/w metronidazole and no holes in sheath layer